



From the INTERNATIONAL SEARCHING AUTHORITY	PCI
To: WOLF, GREENFIELD & SACKS, P.C. Attn. PLUMER, E.R. 600 Atlantic Avenue Boston, Massachusetts 02210 UNITED STATES OF AMERICA Subject to PTA? YES/NO per docket/ECB MMO2 14 01 File Folder ECB Docket Entry Docket Cross Off Order Oppiel Annuties Confinitation?	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION (PCT Rule 44.1)
71	Date of mailing (day/month/year) 13/02/2001
Applicant's or agent's file reference I 0308/7000W0	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 00/ 25877	International filing date (day/month/year) 21/09/2000
Applicant	
ISIS INNOVATION LIMITED et al.	
1. X The applicant is hereby notified that the International Search Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claim When? The time limit for filing such amendments is normal international Search Report; however, for more defined. Where? Directly to the International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	ns of the International Application (see Rule 46):
Fascimile No.: (41–22) 740.14.35 For more detailed instructions, see the notes on the acco	mpanying sheet.
2. The applicant is hereby notified that no International Search Article 17(2)(a) to that effect is transmitted herewith.	n Report will be established and that the declaration under
3. With regard to the protest against payment of (an) addition the protest together with the decision thereon has bee applicant's request to forward the texts of both the pro	onal fee(s) under Rule 40.2, the applicant is notified that: n transmitted to the International Bureau together with the test and the decision thereon to the designated Offices.
no decision has been made yet on the protest; the app	plicant will be notified as soon as a decision is made.
4. Further action(s): The applicant is reminded of the following: Shortly after 18 months from the priority date, the international at if the applicant wishes to avoid or postpone publication, a notice priority claim, must reach the International Bureau as provided completion of the technical preparations for international publication. Within 19 months from the priority date, a demand for internation wishes to postpone the entry into the national phase until 30 months. Within 20 months from the priority date, the applicant must perform before all designated Offices which have not been elected in the	in Rules 90bis.1 and 90bis.3, respectively, before the ation. all preliminary examination must be filed if the applicant on the priority date (in some Offices even later). In the prescribed acts for entry into the national phase are demand or in a later election within 19 months from the
priority date or could not be elected because they are not bound Name and mailing address of the international Searching Authority	Authorized officer

Geertruida Groeneveld-Van der Spek

European Patent Office, P.B. 5818 Patentiaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:

 *Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;
 claims 30, 33 and 36 unchanged; new claims 49 to 51 added.*
- [Where originally there were 15 claims and after amendment of all claims there are 11]:
 "Claims 1 to 15 replaced by amended claims 1 to 11."
- 3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4 [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Adiala 19(1))

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

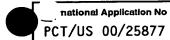
For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification (Form PCT/IS	on of Transmittal of International Search Report 6A/220) as well as, where applicable, item 5 below.
10308/7000WO		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 00/25877	21/09/2000	21/09/1999
Applicant		
ISIS INNOVATION LIMITED e	t al	
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching ansmitted to the International Bureau.	Authority and is transmitted to the applicant
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in	this report.
Basis of the report		
 a. With regard to the language, the language in which it was filed, unl 	international search was carried out on the ess otherwise indicated under this item.	basis of the international application in the
Authority (Rule 23.1(b)).		of the international application furnished to this
was carried out on the basis of the	e sequence listing :	ne International application, the international search
X contained in the internation	onal application in written form.	
filed together with the inte	rnational application in computer readable	form.
furnished subsequently to	this Authority in written form.	
	this Authority in computer readble form.	
the statement that the sub		ng does not go beyond the disclosure in the
		rm is identical to the written sequence listing has been
X the statement that the info	Amadon recorded in computer reducable to	in to dollara to all minor so quality
2. X Certain claims were fou	nd unsearchable (See Box I).	
3. Unity of invention is lac		
g		
4. With regard to the title,		
	hmitted by the applicant	
the text has been establis	hed by this Authority to read as follows:	
5. With regard to the abstract,		
the text is approved as su	bmitted by the applicant.	
the text has been establis	shed, according to Rule 38.2(b), by this Aut	thority as it appears in Box III. The applicant may, n report, submit comments to this Authority.
6. The figure of the drawings to be publ	ished with the abstract is Figure No.	1
as suggested by the appli		None of the figures.
because the applicant fail		
	characterizes the invention.	
Decause this lighte better	CHARACTERIZES ATO THY CHAOTI.	





A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/67 C12Q1/68 G01N33/50 C12N5/10,A01K67/027,A61K38/17

//C12N15/12,C07K14/735,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) $IPC \ 7 \ C07K \ A01K \ C12Q \ A61K$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

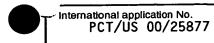
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, STRAND, BIOSIS

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 05481 A (ISIS INNOVATION ;COOKSON WILLIAM OSMOND CHARLES (GB); HOPKIN JULIA) 23 February 1995 (1995-02-23) the whole document	16-18, 20-23, 29-31
Α	US 5 807 988 A (JOUVIN MARIE-HELENE ET AL) 15 September 1998 (1998-09-15) examples 1-14	1-31
Furth	ner documents are listed in the continuation of box C.	members are listed in annex.
"A" docume consid	ent defining the general state of the art which is not let to be of particular relevance invention document but published on or after the international late or priority date and cited to understan invention invention. "X" document of particular cannot be considered.	blished after the international filing date do not in conflict with the application but do the principle or theory underlying the utar retevance; the claimed invention ared novel or cannot be considered to ye step when the document is taken alone

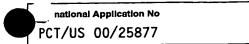
filing date *L* document which may throw doubts on priority dalm(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family	
Date of the actual completion of the international search	Date of mailing of the international search report	
1 February 2001	13/02/2001	
Name and mailing address of the ISA	Authorized officer	
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I	





Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7-15, 28 and, as far as methods in vivo are considered, claims 1-5, 24-26 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTE AATIONAL SEARCH REPORT



Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9505481	Α	23-02-1995	NONE	
US 5807988	Α	15-09-1998	US 5770396 A	23-06-1998
00 0007300	••		AT 169676 T	15-08-1998
			AU 676680 B	20-03-1997
			AU 4283493 A	18-11-1993
			DE 69320336 D	17-09-1998
			DE 69320336 T	08-04-1999
			EP 0636177 A	01-02-1995
			JP 7506486 T	20-07-1995
			WO 9321317 A	28-10-1993